

# Cross-Sectional Associations Between Abdominal and Thoracic Adipose Tissue Compartments and Adiponectin and Resistin in the Framingham Heart Study

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**OBJECTIVE** — To test the association of regional fat depots with circulating adiponectin and resistin concentrations and to assess the potential mediating effect of adipokines on associations between abdominal fat depots and cardiometabolic risk factors.

**RESEARCH DESIGN AND METHODS** — Participants from the Framingham Heart Study offspring cohort ( $n = 916$ , 55% women; mean age 59 years) free of cardiovascular disease underwent computed tomography measurement of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), pericardial fat, and intrathoracic fat volumes and assays of circulating adiponectin and resistin.

**RESULTS** — VAT, SAT, pericardial fat, and intrathoracic fat were negatively correlated with adiponectin ( $r = -0.19$  to  $-0.34$ ,  $P < 0.001$  [women];  $r = -0.15$  to  $-0.26$ ,  $P < 0.01$  [men] except SAT) and positively correlated with resistin ( $r = 0.16$ – $0.21$ ,  $P < 0.001$  [women];  $r = 0.11$ – $0.14$ ,  $P < 0.05$  [men] except VAT). VAT increased the multivariable model  $R^2$  for adiponectin from 2–4% to 10–13% and for resistin from 3–4% to 3–6%. Adjustment for adipokines did not fully attenuate associations between VAT, SAT, and cardiometabolic risk factors.

**CONCLUSIONS** — Adiponectin and resistin are correlated with fat depots cross-sectionally, but none of the adipokines can serve as surrogates for the fat depots. Relations between VAT, SAT, and cardiometabolic risk factors were not fully explained by adiponectin or resistin concentrations.

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The risk of cardiometabolic diseases increases with fat accumulation in ectopic depots (1–5). Visceral adipose tissue (VAT) is more associated with an increased risk of developing diabetes, hypertension, dyslipidemia, and metabolic syndrome compared with subcutaneous adipose tissue (SAT) (1,2). Pericardial fat and intrathoracic fat may also confer addi-

tional metabolic risk (4,5). The increased metabolic risk associated with ectopic fat depots may be due to their associations with adiponectin (6,7). However, prior studies (6–8) have been limited in size or age distribution and used only one or two computed tomography (CT) slices to measure abdominal fat area, which might lead to inaccuracy in measurement of actual regional

fat deposits. In addition, it is not clear whether indexes of regional adiposity contribute to interindividual variation in systemic adipokine concentrations beyond anthropometric measures such as BMI and waist circumference (6–8). In this study, we investigated the cross-sectional associations of regional fat depots and circulating levels of adiponectin and resistin and assessed whether these adipokines mediate the association of abdominal fat depots with cardiometabolic risk factors.

## RESEARCH DESIGN AND METHODS

Participants were selected from the Framingham Heart Study multidetector CT substudy of the community-based Framingham Heart Study offspring cohort; inclusion criteria have been described previously (1). Beginning in 1971, the offspring study enrolled the offspring and spouses of the offspring whose parents were in the original cohort of the Framingham Heart Study. A subset of the offspring cohort had measurements of adipokine concentrations at their seventh examination cycle between 1998 and 2001.

Of 1,418 participants in the offspring cohort of the multidetector CT study, 1,342 participants had interpretable CT measurements of visceral, subcutaneous, pericardial, and intrathoracic fat volume between 2002 and 2005. Plasma adiponectin and resistin concentrations were available in 1,060 of 1,342 participants. After excluding participants with clinically prevalent cardiovascular disease (CVD), prior coronary artery bypass graft, and an incomplete covariate profile, the final sample size was 916 (501 women and 415 men). The institutional review boards of Boston University Medical Center and Massachusetts General Hospital approved this study. Written informed consent was obtained from all participants.

## Adipokine measurements

Circulating concentrations of adiponectin and resistin were measured by enzyme-

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linked immunosorbent assay (R&D Systems, Minneapolis, MN) in plasma collected after a >8-h fast and frozen at  $-80^{\circ}\text{C}$ . Intra-assay coefficients of variation were 5.8% for adiponectin and 9.0% for resistin. Single, random plasma adiponectin and resistin concentrations have been shown to be stable over a 1-year period (9).

### Volumetric adipose tissue imaging

An 8-slice multidetector CT (LightSpeed Ultra; General Electric, Milwaukee, WI) was used to image the abdomen and thorax. While lying in a supine position, participants had an average of 25 contiguous 5-mm-thick cross-sectional images (120 kVp; 40 mA; gantry rotation time, 500 ms; table feed, 3:1) of the abdomen and 48 contiguous 2.5-mm-thick cross-sectional images of the heart (120 kVp; 400 mA; temporal resolution, 330 ms). The abdominal images spanned 125 mm above the level of S1. The specific protocols used to obtain images of the abdomen and thorax have been described elsewhere (5,10).

### Abdominal and thoracic adipose tissue measurements

Visceral, subcutaneous, pericardial, and thoracic fat volumes were measured (Aquarius 3D Workstation; TeraRecon, San Mateo, CA) using an image display window width of  $-195$  to  $-45$  Hounsfield units (HU) and window center of  $-120$  HU. The readers manually traced the abdominal muscular wall separating the visceral and subcutaneous depots and outlined the pericardium to distinguish pericardial from thoracic fat. Pericardial fat volume included all adipose tissue visualized within the pericardial sac. Total thoracic fat volume consisted of adipose tissue from the right pulmonary artery to the diaphragm and from the chest wall to the descending aorta, including fat within the pericardial sac. Interreader reproducibility was excellent for visceral, subcutaneous, pericardial, and thoracic fat volume measurements (1,10). Intrathoracic fat was derived after subtracting pericardial fat from total thoracic fat to identify two mutually exclusive fat compartments.

### Risk factor and covariate assessment

Cardiometabolic risk factors and other covariates were assessed at the contemporaneous examination. BMI was measured as weight (in kilograms) divided by the square of height (in meters). Waist cir-

cumference was measured at the level of the umbilicus. Tobacco and alcohol use were self-reported through physician-administered questions. Participants were classified as current smokers if they smoked on average at least one cigarette per day in the previous year. Women who drank  $\geq 7$  alcoholic drinks per week and men who consumed  $\geq 14$  alcoholic drinks per week were considered alcohol users. The physical activity index was based on the average number of hours per day spent sleeping and doing sedentary, slight, moderate, and heavy activity. Women were considered postmenopausal if they had not had any menstrual periods for at least 1 year.

Hypertension was diagnosed as a systolic blood pressure  $\geq 140$  mmHg, a diastolic blood pressure  $\geq 90$  mmHg, or treatment with antihypertensive agents. Fasting morning plasma samples were collected to measure fasting plasma glucose, total cholesterol, HDL cholesterol, and triglycerides. Diabetes was defined as a fasting plasma glucose  $\geq 126$  mg/dl ( $\geq 7$  mmol/l) or treatment with insulin or a hypoglycemic medication. Metabolic syndrome was defined based on modified Adult Treatment Plan III criteria.

### Statistical analysis

Adiponectin, VAT, SAT, pericardial fat, and intrathoracic fat volumes were approximately normally distributed. Resistin was logarithmically transformed to normalize the distribution. All analyses were a priori performed specific to sex due to strong sex interactions we had previously observed with SAT and VAT (1). Sex-specific and age-adjusted Pearson correlation coefficients were calculated to determine the correlation between each fat compartment, adiponectin, and log resistin.

Sex-specific multivariable linear regression was used to evaluate the associations of adiponectin and log resistin (dependent variables; separate models for each) with fat depots (independent variables), after adjustment for age, smoking, alcohol use, menopausal status (women only), and hormone replacement therapy (women only). VAT, SAT, pericardial fat, and intrathoracic fat were standardized to a means  $\pm$  SD of  $0 \pm 1$ ; the covariate-adjusted average change in adiponectin and log resistin per SD of adipose tissue volume was estimated. Using this approach, the multivariable regression results for each fat compartment could be more directly compared. The multivariable models for VAT, pericardial fat, and

intrathoracic fat were then additionally adjusted for BMI and waist circumference in order to assess whether relations were maintained after adjusting for measures of generalized adiposity. As secondary analyses, multivariable models for VAT, SAT, pericardial fat, and intrathoracic fat were also additionally adjusted for physical activity and education status.

Multivariable linear and logistic regressions were used to relate VAT and SAT (independent variables) to cardiometabolic risk factors (dependent variables). Models for systolic blood pressure, fasting plasma glucose, log triglycerides, HDL cholesterol, and metabolic syndrome were evaluated (separate model for each risk factor). Age, smoking, alcohol use, menopausal status (women only), hormone replacement therapy (women only), and treatment of hypertension, dyslipidemia, and diabetes were entered as covariates in each of the models. Each multivariable model was also adjusted for either adiponectin or log resistin (separate models for each adjustment) to assess the extent of attenuation of the association of VAT and SAT with each cardiometabolic risk factor upon adjustment for these adipokines. All analyses were performed using SAS version 9.1. A two-tailed value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Study sample characteristics

Overall, 916 participants were available for analysis. The mean age was 59 years (Table 1), and slightly more than one-quarter were obese. The majority of women were postmenopausal.

### Age-adjusted correlations between fat depots and adipokines

VAT, SAT, pericardial fat, and intrathoracic fat were negatively correlated with adiponectin ( $r = -0.19$  to  $-0.34$ ,  $P < 0.001$  [women];  $r = -0.15$  to  $-0.26$ ,  $P < 0.01$  [men] except SAT) and positively correlated with resistin ( $r = 0.16$ – $0.21$ ,  $P < 0.001$  [women];  $r = 0.11$ – $0.14$ ,  $P < 0.05$  [men] except VAT) (Table 2).

### Multivariable-adjusted regressions with fat depots and adiponectin

In women, adiponectin concentration was  $2.1 \pm 0.3$   $\mu\text{g/ml}$  lower per SD increase of VAT,  $1.2 \pm 0.3$   $\mu\text{g/ml}$  lower per SD increase of SAT,  $1.2 \pm 0.3$   $\mu\text{g/ml}$  lower per SD increase of pericardial fat,

Table 1—Clinical characteristics of 916 study participants

	Women	Men
n	501	415
Age (years)	59 ± 9	59 ± 9
BMI (kg/m <sup>2</sup> )	27.8 ± 5.3	28.8 ± 4.4
Waist circumference (inches)	38 ± 6	41 ± 4
Obesity (%)	28.1	29.4
Triglycerides (mg/dl)	109 (77–163)	116 (77–174)
HDL cholesterol (mg/dl)	61 ± 16	46 ± 12
Total cholesterol (mg/dl)	206 ± 36	195 ± 33
Dyslipidemia treatment (%)	14.4	15.2
Systolic blood pressure (mmHg)	124 ± 20	127 ± 16
Hypertension (%)	36.1	40.0
Hypertension treatment (%)	26.4	26.3
Fasting plasma glucose (mg/dl)	98 ± 17	105 ± 24
Diabetes (%)	7.2	10.8
Metabolic syndrome (%)	38.3	41.9
Physical activity index	37.4	38.2
Smoking (%)		
Current	41.5	39.3
Former	47.7	51.1
Never	10.8	14.9
Alcohol use (%)*	16.0	14.9
Postmenopausal (%)	81.6	—
Hormone replacement therapy (%)	36.9	—
C <sub>T</sub> fat measures (cm <sup>3</sup> )		
Visceral fat	1,627 ± 869	2,539 ± 1,045
Subcutaneous fat	3,350 ± 1,378	2,676 ± 1,124
Pericardial fat	109 ± 40	135 ± 51
Intrathoracic fat	85 ± 43	146 ± 63
Adiponectin (μg/ml)	11.0 (7.6–16.5)	6.3 (4.2–9.0)
Resistin (ng/ml)	13.1 (10.5–16.3)	13.0 (10.3–17.0)

Data are means ± SD or median (25th–75th percentile). \*Defined as ≥7 drinks/week (for women) or ≥14 drinks/week (for men). Conversion to SI units: multiply waist circumference by 2.54 for cm, triglycerides by 0.01129 for mmol/l, HDL and total cholesterol by 0.02586 for mmol/l, and fasting plasma glucose by 0.05551 for mmol/l.

and 1.2 ± 0.3 μg/ml lower per SD increase of intrathoracic fat ( $P < 0.001$ ) in multivariable-adjusted models (Table 3). The regression coefficients for adiponectin concentration were larger per SD of VAT than per SD of SAT ( $P < 0.001$ ). In men, the multivariable-adjusted effect sizes of VAT, SAT, pericardial fat, and intrathoracic fat on adiponectin concentra-

tion were weaker but still significant in nearly all cases (Table 3). A sex-by-VAT interaction was observed for adiponectin ( $P < 0.001$ ), as well as a sex-by-SAT ( $P = 0.001$ ) and sex-by-pericardial fat interaction ( $P = 0.03$ ).

In women, VAT remained associated with adiponectin after additional adjustment for BMI and waist circumference

( $P = <0.001$ ); pericardial fat and intrathoracic fat did not remain associated with adiponectin ( $P = 0.15$  [pericardial fat],  $P = 0.5$  [intrathoracic fat]). In contrast, among men, VAT, pericardial fat, and intrathoracic fat were associated with adiponectin after further adjustment for BMI and waist circumference (all  $P < 0.02$ ).

Covariates (age, sex, smoking, alcohol use, menopausal status, and hormone replacement therapy) explained 2% of the circulating variability in adiponectin concentration in women and 4% in men; adding VAT to this model increased the model  $R^2$  to 13% in women and 10% in men (Table 3). Multivariable-adjusted models for SAT, pericardial fat, and intrathoracic fat accounted for a smaller portion of the variation in adiponectin concentration ( $R^2$  range 4–8%).

### Multivariable-adjusted regressions with fat depots and resistin

VAT, SAT, pericardial fat, and intrathoracic fat were associated with resistin. Sex interactions were not observed (all  $P > 0.1$ ). In women, additional adjustment for BMI and waist circumference attenuated associations between VAT, pericardial fat, intrathoracic fat, and resistin (all  $P > 0.2$ ). Results were similar for men, except intrathoracic fat remained associated with resistin after additional adjustment for BMI and waist circumference ( $P = 0.02$ ). None of the multivariable-adjusted models explained a substantial portion of the variability in resistin concentration ( $R^2$  range 3–6%).

### Secondary analyses

When physical activity and education status were included as additional covariates, relations between adipose tissue volumes, adiponectin, and resistin were not materially different (data not shown).

### Multivariable-adjusted regressions with VAT, SAT, and cardiometabolic risk factors additionally adjusted for adipokines

VAT was associated with all cardiometabolic risk factors in both sexes as previously reported (1), except for systolic blood pressure in men (online appendix Tables 1A and 1B [available at <http://care.diabetesjournals.org/cgi/content/full/dc08-1733/DC1>]).

In women, we observed some attenuation of the effect size of VAT on log triglycerides and HDL cholesterol after

Table 2—Age-adjusted Pearson correlation coefficients between fat depot volumes and adipokines

	Women		Men	
	Adiponectin	Log resistin	Adiponectin	Log resistin
n	501	501	415	415
Visceral fat	−0.34*	0.16*	−0.26*	0.08
Subcutaneous fat	−0.21*	0.17*	−0.02	0.13†
Pericardial fat	−0.19*	0.16*	−0.15†	0.11‡
Intrathoracic fat	−0.21*	0.21*	−0.22*	0.14†

\* $P < 0.001$ ; † $P < 0.01$ ; ‡ $P < 0.05$ .

Table 3—Sex-specific multivariable-adjusted\* regressions for fat depot volumes with adipokines

	Women			Men			P‡
	Effect size†	R <sup>2</sup> (%)	P	Effect size†	R <sup>2</sup> (%)	P	
Adiponectin§							
Visceral fat	−2.1 (−1.5 to −2.7)	13	<0.001	−1.1 (−0.7 to −1.5)	10	<0.001	<0.001
Subcutaneous fat	−1.2 (−0.6 to −1.8)	6	<0.001	0.1 (−0.3 to 0.5)	4	0.54	0.001
Pericardial fat	−1.2 (−0.6 to −1.8)	6	<0.001	−0.6 (−0.2 to −1.0)	6	0.005	0.03
Intrathoracic fat	−1.2 (−0.6 to −1.8)	5	<0.001	−0.9 (−0.5 to −1.3)	8	<0.001	0.07
Log resistin							
Visceral fat	1.06 (1.03–1.10)	6	<0.001	1.04 (1.00–1.08)	3	0.07	0.15
Subcutaneous fat	1.06 (1.03–1.10)	6	<0.001	1.05 (1.01–1.10)	4	0.008	0.88
Pericardial fat	1.04 (1.00–1.08)	5	0.03	1.05 (1.01–1.10)	4	0.01	0.77
Intrathoracic fat	1.06 (1.02–1.09)	6	0.002	1.07 (1.03–1.11)	5	0.002	0.43

\*Adjusted for age, smoking, alcohol use, menopausal status (women only), and hormone replacement therapy (women only). †Effect size refers to the average change in adiponectin or resistin concentration per SD of visceral, subcutaneous, pericardial, or intrathoracic fat volume. Effect sizes for log resistin were back transformed to a nonlogarithmic scale. ‡P value for sex interaction obtained from multivariable regression analysis on entire sample, adjusted for sex, age, smoking, alcohol use, menopausal status (women only), hormone replacement therapy (women only), and a sex-by-fat interaction term. §R<sup>2</sup> of model with covariates only is 2% in women and 4% in men. ||R<sup>2</sup> of model with covariates only is 4% in women and 3% in men.

additional adjustment for adiponectin, but strong associations were still observed. After multivariable adjustment, HDL cholesterol was  $5.1 \pm 0.7$  mg/dl ( $0.13 \pm 0.02$  mmol/l) lower per SD increase of VAT. After further adjustment for adiponectin, HDL cholesterol was  $3.1 \pm 0.6$  mg/dl ( $0.08 \pm 0.02$  mmol/l) lower per SD increase of VAT. Fasting plasma glucose and diabetes did not appreciably change after adjustment for adiponectin. For SAT, similar results were observed.

In men, there was more attenuation of the effect size of VAT on fasting plasma glucose, but not for diabetes, after additional adjustment for adiponectin. The effect size of VAT on HDL cholesterol was minimally weakened after additional adjustment for adiponectin. Relations between VAT, log triglycerides, and metabolic syndrome, as well as between SAT and cardiometabolic risk factors, did not appreciably change after adjustment for adiponectin in men. None of the associations between VAT, SAT, and cardiometabolic risk factors appreciably changed upon adjustment for resistin (online appendix Tables 1A and 1B).

**CONCLUSIONS**— In the community-based Framingham offspring cohort, VAT, SAT, pericardial fat, and intrathoracic fat were negatively correlated with adiponectin but positively correlated with resistin. For both sexes, the strongest correlation was between VAT and adiponectin, but the correlation coefficients were still weak. Furthermore, the addition of VAT only increased the model R<sup>2</sup> for adiponectin from 2–4% to 10–13%. VAT is

not a primary determinant of systemic total adiponectin concentration, and circulating levels of adiponectin cannot be used as a surrogate for VAT. Adjustment for adiponectin attenuated relations between VAT, SAT, and cardiometabolic risk factors, but adiponectin did not fully account for the strong relations between VAT and cardiometabolic risk factors. Easily obtainable anthropometric measures (BMI and waist circumference) did not explain the associations between VAT and adiponectin in women or men and between pericardial fat, intrathoracic fat, and adiponectin in men. Therefore, ectopic fat depots may provide some additional insight about systemic adiponectin concentrations not apparent with measures of general adiposity.

The modest inverse association between VAT and adiponectin has been observed previously (6,8,11). We observed strong sex interactions in the effect size of VAT on systemic adiponectin concentration. Other studies have demonstrated significant sex interactions in the associations between VAT and cardiometabolic risk factors (1,7). VAT may have higher lipolytic activity in women compared with men (12). Sex differences in free fatty acid delivery to the liver may account for the observed sex interactions, but the mechanisms are still not clear.

The associations between fat depots and resistin have not been extensively studied. The role of resistin in human obesity is controversial, but a recent candidate gene study (13) suggests an association between resistin and regional fat distribution and metabolic complications in HIV lipodystrophy. We were able to

observe small but significant associations between fat depots and resistin.

The strong relations between VAT, diabetes, dyslipidemia, hypertension, and metabolic syndrome have been observed previously. The results of the present study reveal that adiponectin does not fully explain the relations between VAT, systolic blood pressure, diabetes, and metabolic syndrome. The associations between VAT, log triglycerides, HDL cholesterol, and fasting plasma glucose were attenuated, but not fully accounted for, by adiponectin. These findings contrast with prior work in the Health, Aging, and Body Composition Cohort, where the association between VAT and diabetes in a multivariable model was minimally attenuated by adjustment for combination of adiponectin, leptin, and plasminogen activator inhibitor-1 (11). However, PAI-1 was the only adipokine found to be independently associated with incident diabetes. Given the modest correlations between VAT, SAT, and adiponectin, it is not surprising that we did not observe more attenuation in these models. Adjustment for resistin did not weaken any of the associations between VAT and cardiometabolic risk factors.

The differential associations between VAT, SAT, and adiponectin may be explained by differential adipocyte adipokine production and regulatory feedback of local inflammatory signals. Several small studies in lean and obese nondiabetic participants have shown that adiponectin mRNA levels are lower in VAT compared with SAT (14,15), although these findings are not universal (16). VAT is associated with several inflammatory



markers, even after adjustment for BMI and waist circumference (17). Tumor necrosis factor- $\alpha$ , interleukin-6, and C-reactive protein can suppress adiponectin gene expression. In addition, adiponectin binds to complement factors and injured vessel walls (18); therefore, adiponectin concentrations may be further reduced in the presence of a high VAT volume and systemic inflammation. In humans, resistin is primarily derived from macrophages that have infiltrated adipose tissue (19). A rodent study (20) revealed that macrophage content is higher in VAT compared with SAT in *db/db* mice but had similar concentrations in control mice.

Given the modest correlations between VAT and adiponectin, adiponectin does not appear to be a good serum proxy for VAT. Adjustment for adiponectin affected relations between VAT and fasting plasma glucose in men, HDL cholesterol, and log triglycerides, albeit minimally. These findings suggest that additional circulating biomarkers and hormones may mediate the relations between VAT and cardiometabolic risk factors. It is also possible that high molecular weight adiponectin, rather than total adiponectin, may be a more potent mediator of the associations between VAT and cardiometabolic risk factors.

The strengths of this study include a well-characterized study sample and precise volumetric quantification of adipose tissue. The limitations include the cross-sectional design of the study, lack of ethnic diversity, noncontemporaneous CT and adipokine concentrations, and adiponectin assay. Given the cross-sectional, observational nature of our study design, causality cannot be inferred. Because the sample is comprised of primarily white participants, generalizability to other ethnic groups is uncertain. Adipokine concentrations, as well as glucose, cholesterol, and anthropometric measurements, were obtained several years before the CTs were performed. Serum adiponectin levels and cardiometabolic risk factors may have changed at the time of the CTs, and regional fat depot measurements may have been different at the time of adipokine concentrations. However, adipokine measurements have been shown to be stable over a 1-year period (9). Nonetheless, we cannot rule out misclassification based on the 4-year time lag between the adipokine and CT measurements that may have affected our results. Any minor variation in adipokine measurements should not impact the relative association among

VAT, SAT, pericardial fat, intrathoracic fat, and adipokines, which is the primary focus of this study. We measured systemic levels and not local adipokine concentrations, and systemic levels may not reflect local production and release by all regional fat depots. Adipokines produced by VAT are released into portal circulation, where hormones can be metabolized. Therefore, systemic adiponectin concentration may underestimate adiponectin concentration that is actually secreted by VAT. However, a recent study did not demonstrate a difference between portal and systemic adiponectin concentrations (21); therefore, this is unlikely to explain our results. Lastly, high molecular weight adiponectin is more strongly associated with regional adiposity and metabolic diseases than total adiponectin (22). Thus, our results may have been stronger if we had measured high molecular weight adiponectin instead of total adiponectin. Adiponectin and resistin are correlated with fat depots cross-sectionally, but none of these adipokines can serve as surrogates for these fat depots. Relations among VAT, SAT, and cardiometabolic risk factors were not fully explained by adiponectin or resistin concentrations.

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